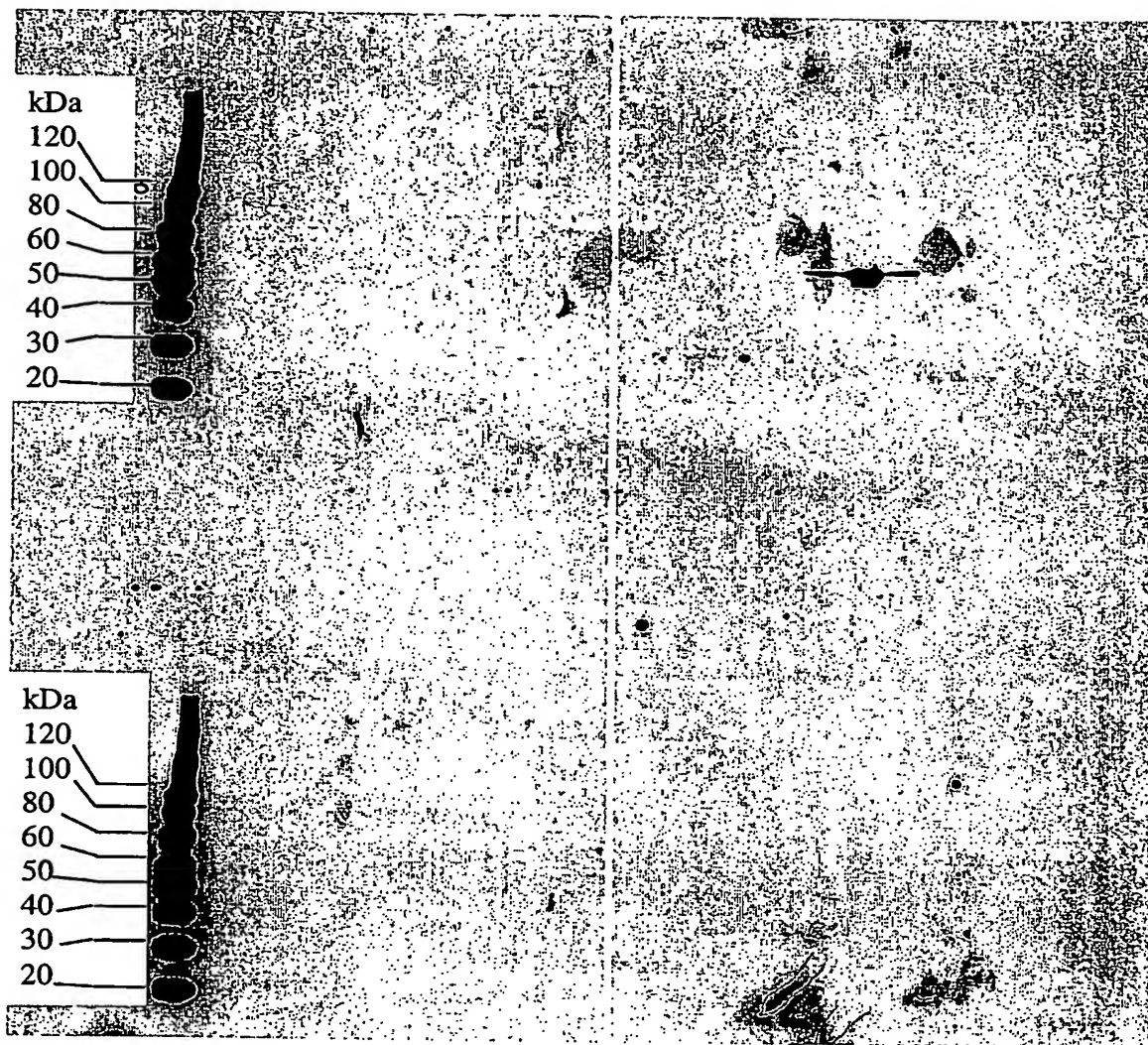


Figure 1 a

Detection of PDE4D7

Media and intima, balloon-injured, left carotis

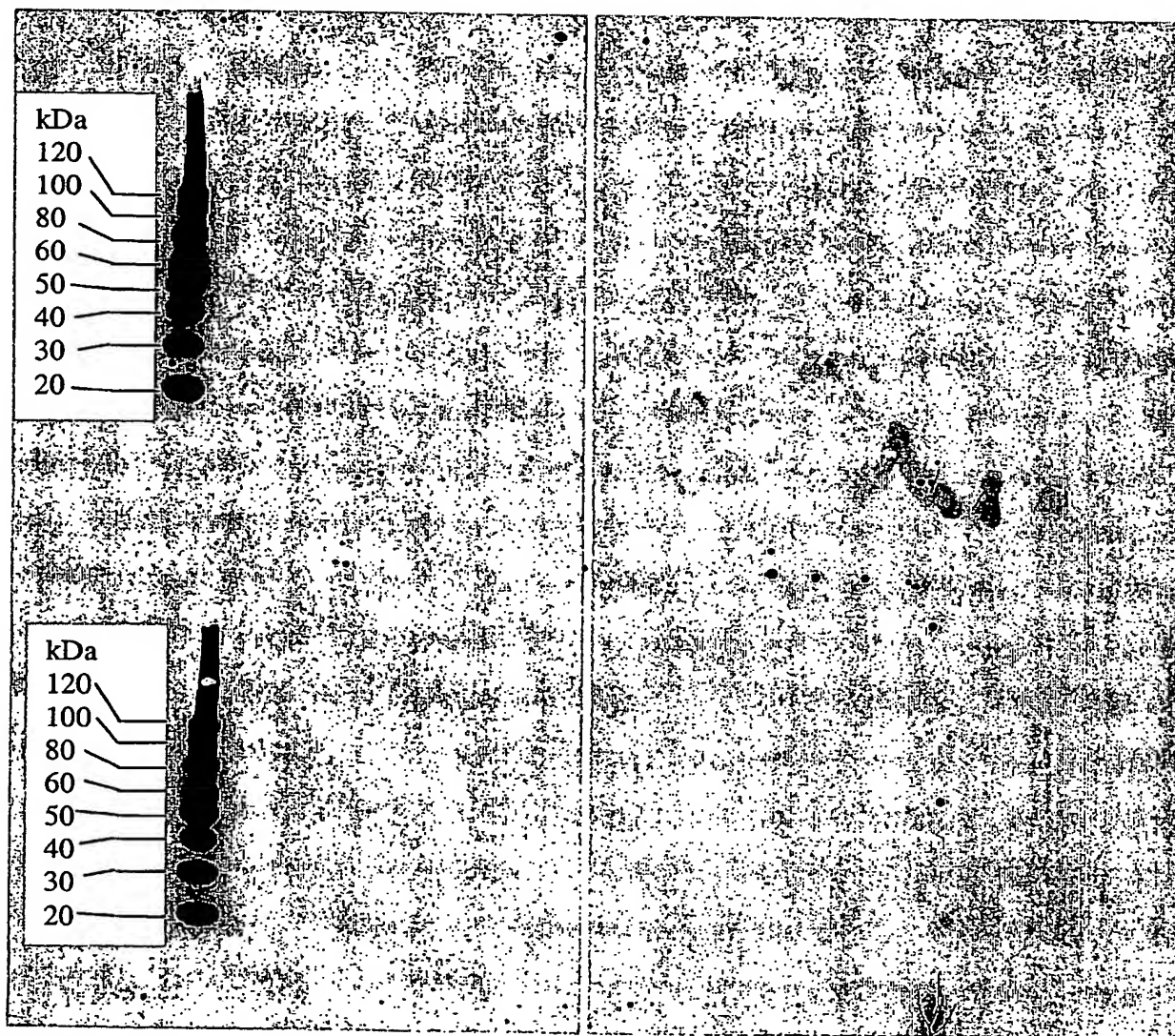


Media, non-injured, right carotis

Figure 1 b

Detection of PDE4D7

Media, non-injured, left carotis



Media, non-injured, right carotis

Figure 2

A. 4D5 N-terminus in man and rat

4D5 N-terminus: 98.85% identical

HUM.seq x RAT.seq

April 1, 2003 17:04 ..

```

      1 MAQQ.TSPDTLTVPEVDNPHCPNPWLNEDLVKSLRENLLQHEKSKTARKS 49
      ||| ||||| ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
      1 MAQQTTSPDTLTVPEVDNPHVNPWLNEDLVKSLRENLLQHEKSKTARKS 50

      50 VSPKLSFVISPRNSPRLRLRMLLSSNIPKQRRFTVAHT 87
      ||||| ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
      51 VSPKLSFVISPRNSPRLRLRMLLSSNIPKQRRFTVAHT 88

```

B. Conserved sequence elements in the human PDE4 gene family

Comparisons:

UCR1

	A	B	C	D
A	+	83.1	79.3	79.7
B		+	79.3	86.4
C			+	86.2
D				+

UCR2

	A	B	C	D
A	+	88.6	78.2	84.8
B		+	79.5	89.9
C			+	83.3
D				+

Catalytic domain

	A	B	C	D
A	+	86.3	82.1	85.2
B		+	80.1	87.4
C			+	84.6
D				+

Figure 3/1

Q8CG05 - Mouse; Q8CG04 - Rat; Q8IVD2 - Human

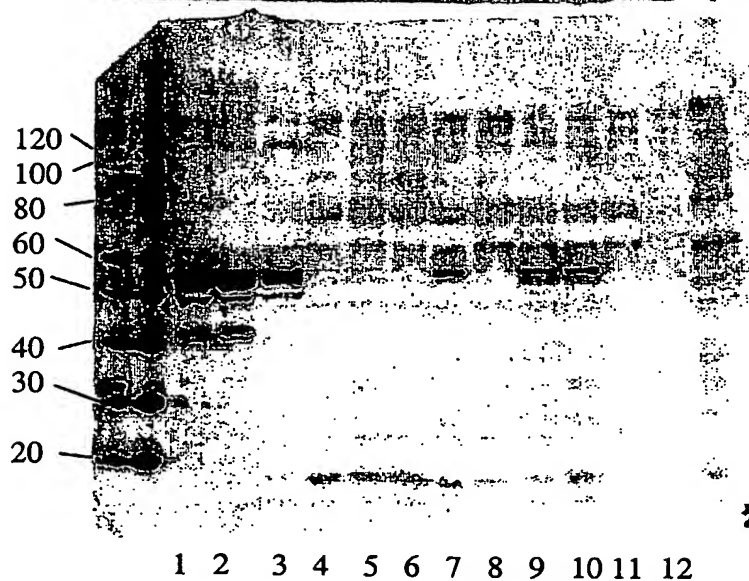
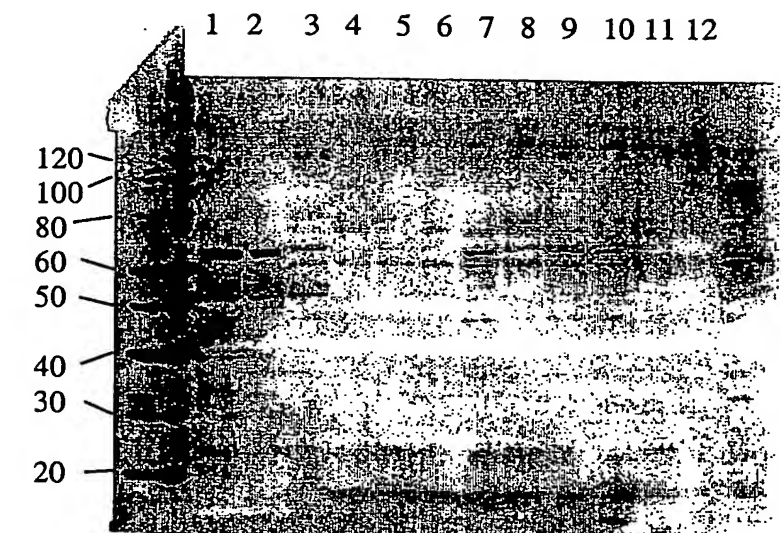
TR_ROD_Q8CG05	MERDTCDVLS	RSKSASEETL	HSCNEEDDPF	RGMEPYLVRR	LSSRSIQLPP
TR_ROD_Q8CG04	MERNTCDVLS	RSKSASEETL	HSCNDEEDPF	RGMEPYLVRR	LSSRSIQLPP
TR_HUM_Q8IVD2	MKRNTCDLLS	RSKSASEETL	HSSNEEDDPF	RGMEPYLVRR	LSCRNIQLPP
TR_ROD_Q8CG05	<u>LAFRQLEQAD</u>	<u>LRSESENIPR</u>	<u>PTSLPLKILP</u>	LIAVTSADSS	GFDVDNGTSA
TR_ROD_Q8CG04	<u>LAFRQLEQTD</u>	<u>LRSESENIPR</u>	<u>PTSLPLKILP</u>	LIAVTSADST	GFDVDNGTSA
TR_HUM_Q8IVD2	<u>LAFRQLEQAD</u>	<u>LKSESENIQR</u>	<u>PTSLPLKILP</u>	LIAITSAESS	GFDVDNGTSA
TR_ROD_Q8CG05	GRSPDPMTS	PGSGLILQAN	FVHSQRRESF	LYRSDSDYDL	SPKSMSRNSS
TR_ROD_Q8CG04	GRSPDPMTS	PGSGLILQAN	FVHSQRRESF	LYRSDSDYDL	SPKSMSRNSS
TR_HUM_Q8IVD2	GRSPDPMTS	PGSGLILQAN	FVHSQRRESF	LYRSDSDYDL	SPKSMSRNSS
TR_ROD_Q8CG05	IASDIHGDDL	IVTPFAQVLA	SLRTVRNNFA	ALTNLQDRAP	SKRSPMCNQF
TR_ROD_Q8CG04	IASDIHGDDL	IVTPFAQVLA	SLRTVRNNFA	ALTNLQDRAP	SKRSPMCNQF
TR_HUM_Q8IVD2	IASDIHGDDL	IVTPFAQVLA	SLRTVRNNFA	ALTNLQDRAP	SKRSPMCNQF
TR_ROD_Q8CG05	SINKATITEE	AYQKLASETL	EELDWCLDQL	ETLQTRHSVS	EMASNKFKRM
TR_ROD_Q8CG04	SINKATITEE	AYQKLASETL	EELDWCLDQL	ETLQTRHSVS	EMASNKFKRM
TR_HUM_Q8IVD2	SINKATITEE	AYQKLASETL	EELDWCLDQL	ETLQTRHSVS	EMASNKFKRM
TR_ROD_Q8CG05	LNRELTHLSE	MSRSGNQVSE	YISNTFLDKQ	HEVEIPSPTQ	KEKEKKKRPM
TR_ROD_Q8CG04	LNRELTHLSE	MSRSGNQVSE	YISNTFLDKQ	HEVEIPSPTQ	KEKEKKKRPM
TR_HUM_Q8IVD2	LNRELTHLSE	MSRSGNQVSE	FISNTFLDKQ	HEVEIPSPTQ	KEKEKKKRPM
TR_ROD_Q8CG05	SQISGVKKLM	HSSSLTNSCI	PRFGVKTEQE	DVLAKELEDV	NKWGLHVFRI
TR_ROD_Q8CG04	SQISGVKKLM	HSSSLTNSCI	PRFGVKTEQE	DVLAKELEDV	NKWGLHVFRI
TR_HUM_Q8IVD2	SQISGVKKLM	HSSSLTNSSI	PRFGVKTEQE	DVLAKELEDV	NKWGLHVFRI
TR_ROD_Q8CG05	AELSGNRPLT	VIMHTIFQER	DLLKTFKIPV	DTLITYLMTL	EDHYHADVAY
TR_ROD_Q8CG04	AELSGNRPLT	VIMHTIFQER	DLLKTFKIPV	DTLITYLMTL	EDHYHADVAY
TR_HUM_Q8IVD2	AELSGNRPLT	VIMHTIFQER	DLLKTFKIPV	DTLITYLMTL	EDHYHADVAY
TR_ROD_Q8CG05	HNNIHAADV	QSTHVLLSTP	ALEAVFTDLE	ILAAIFASAI	HDVDHPGVSN
TR_ROD_Q8CG04	HNNIHAADV	QSTHVLLSTP	ALEAVFTDLE	ILAAIFASAI	HDVDHPGVSN
TR_HUM_Q8IVD2	HNNIHAADV	QSTHVLLSTP	ALEAVFTDLE	ILAAIFASAI	HDVDHPGVSN

Figure 3/2

TR_ROD_Q8CG05	QFLINTNSEL	ALMYNDSSVL	ENHHLAVGFK	LLQEENCDF	QNLTKKQRS
TR_ROD_Q8CG04	QFLINTNSEL	ALMYNDSSVL	ENHHLAVGFK	LLQEENCDF	QNLTKKQRS
TR_HUM_Q8IVD2	QFLINTNSEL	ALMYNDSSVL	ENHHLAVGFK	LLQEENCDF	QNLTKKQRS
TR_ROD_Q8CG05	LRKMVIDIVL	ATDMSKHMNL	LADLKTVMET	KKVTSSGVLL	LDNYSRIQV
TR_ROD_Q8CG04	LRKMAIDIVL	ATDMSKHMNL	LADLKTVMET	KKVTSSGVLL	LDNYSRIQV
TR_HUM_Q8IVD2	LRKMVIDIVL	ATDMSKHMNL	LADLKTVMET	KKVTSSGVLL	LDNYSRIQV
TR_ROD_Q8CG05	LQNMVHCADL	SNPTKPLQLY	RQWTDRIEE	FFRQGDRE	RGMEISPMCD
TR_ROD_Q8CG04	LQNMVHCADL	SNPTKPLQLY	RQWTDRIEE	FFRQGDRE	RGMEISPMCD
TR_HUM_Q8IVD2	LQNMVHCADL	SNPTKPLQLY	RQWTDRIEE	FFRQGDRE	RGMEISPMCD
TR_ROD_Q8CG05	KHNASVEKSQ	VGFDYIVHP	LWETWADLVH	PDAQDILDTL	EDNREWYQST
TR_ROD_Q8CG04	KHNASVEKSQ	VGFDYIVHP	LWETWADLVH	PDAQDILDTL	EDNREWYQST
TR_HUM_Q8IVD2	KHNASVEKSQ	VGFDYIVHP	LWETWADLVH	PDAQDILDTL	EDNREWYQST
TR_ROD_Q8CG05	IPQSPSPAPD	DQEGRQGQT	EKFQFELTLE	EDGESDTEKD	SGSQVEEDTS
TR_ROD_Q8CG04	IPQSPSPAPD	DQEGRQGQT	EKFQFELTLE	EDGESDTEKD	SGSQVEEDTS
TR_HUM_Q8IVD2	IPQSPSPAPD	DQEGRQGQT	EKFQFELTLE	EDGESDTEKD	SGSQVEEDTS
TR_ROD_Q8CG05	CSDSKTLCTQ	DSESTEIPLD	EQVEEEAVAE	EE.SQPETCV	PDDCCPDT
TR_ROD_Q8CG04	CSDSKTLCTQ	DSESTEIPLD	EQVEEEAVAE	EE.SQPQTGV	ADDCCPDT
TR_HUM_Q8IVD2	CSDSKTLCTQ	DSESTEIPLD	EQVEEEAVGE	EEESQPEACV	IDDRSPDT

Figure 4:

anti-PDE4D5



anti-PDE4D7

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Figure 5

fluorescence polarization assay
30ng/ml PDE4D core construct IC₅₀ Rolipram @40nMcAMP

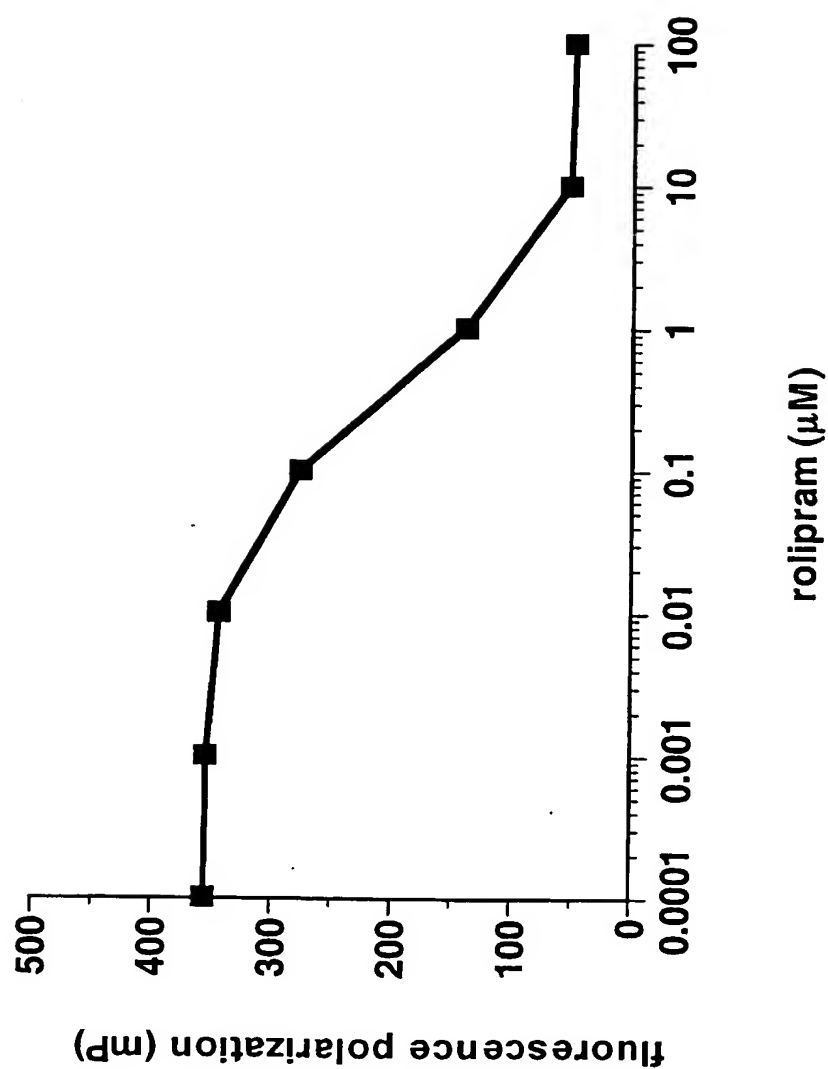
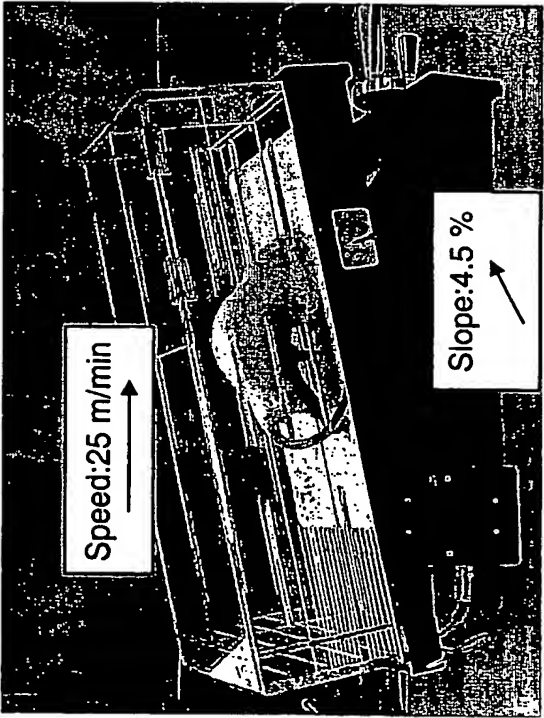


Figure 6

	L/R FEMORAL ARTERY INJECTION	TREATMENT (p.o)
Group 1 (n=12)	Sham operated	Placebo (vehicle)
Group 3 (n=12)	Lauric Acid (75 µg)	Placebo (vehicle)
Group 3 (n=12)	Lauric Acid (75 µg)	Cilomilast (8 mg/kg/day)*
Group 4 (n=12)	Lauric Acid (75 µg)	Cilostazol (100 mg/kg/day)*

*first dose administered 24 h and 2 h pre-LA injection

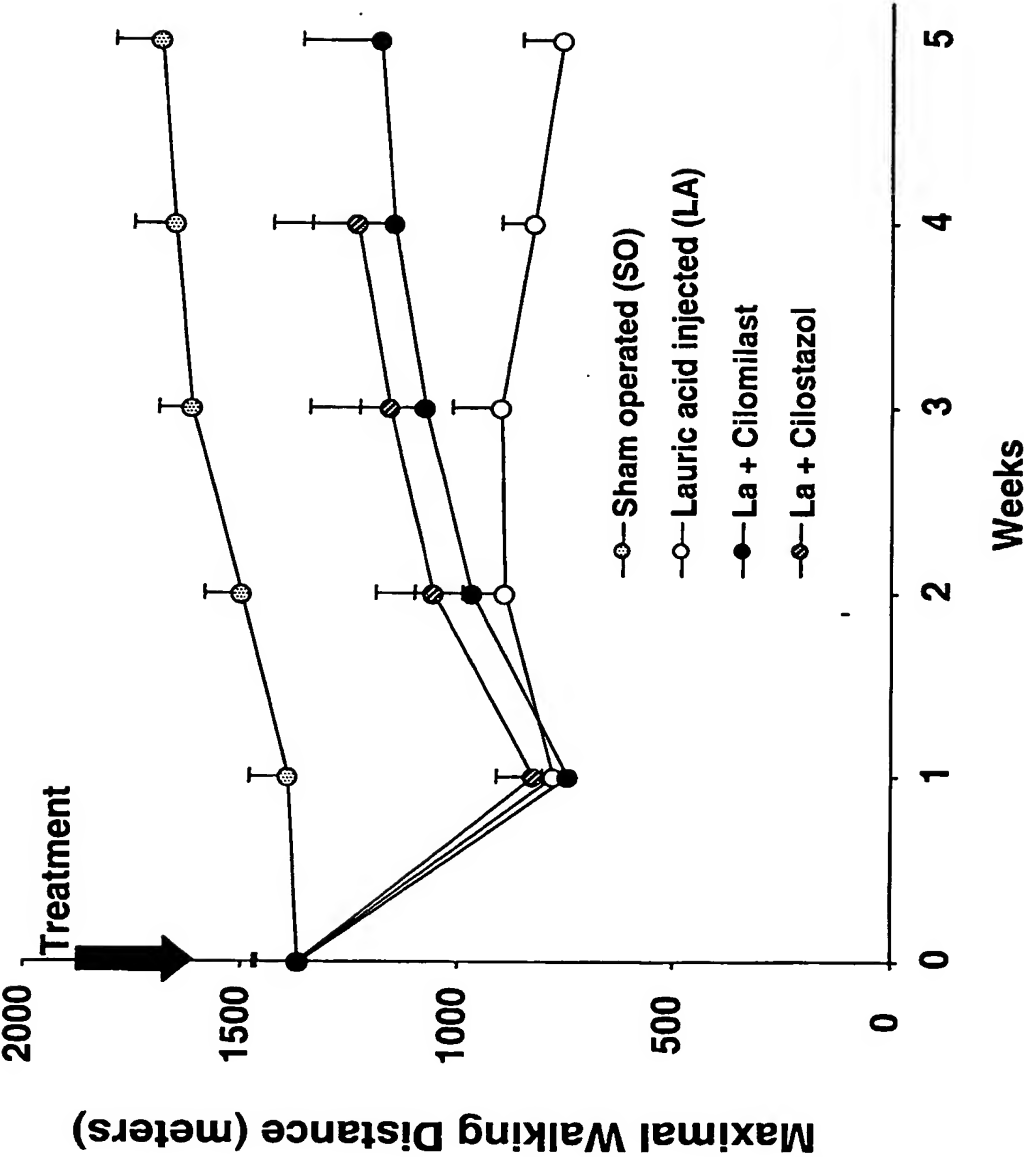


TREADMILL

WEEK 1- 2- 3- 4- 5
post-lauric acid injection

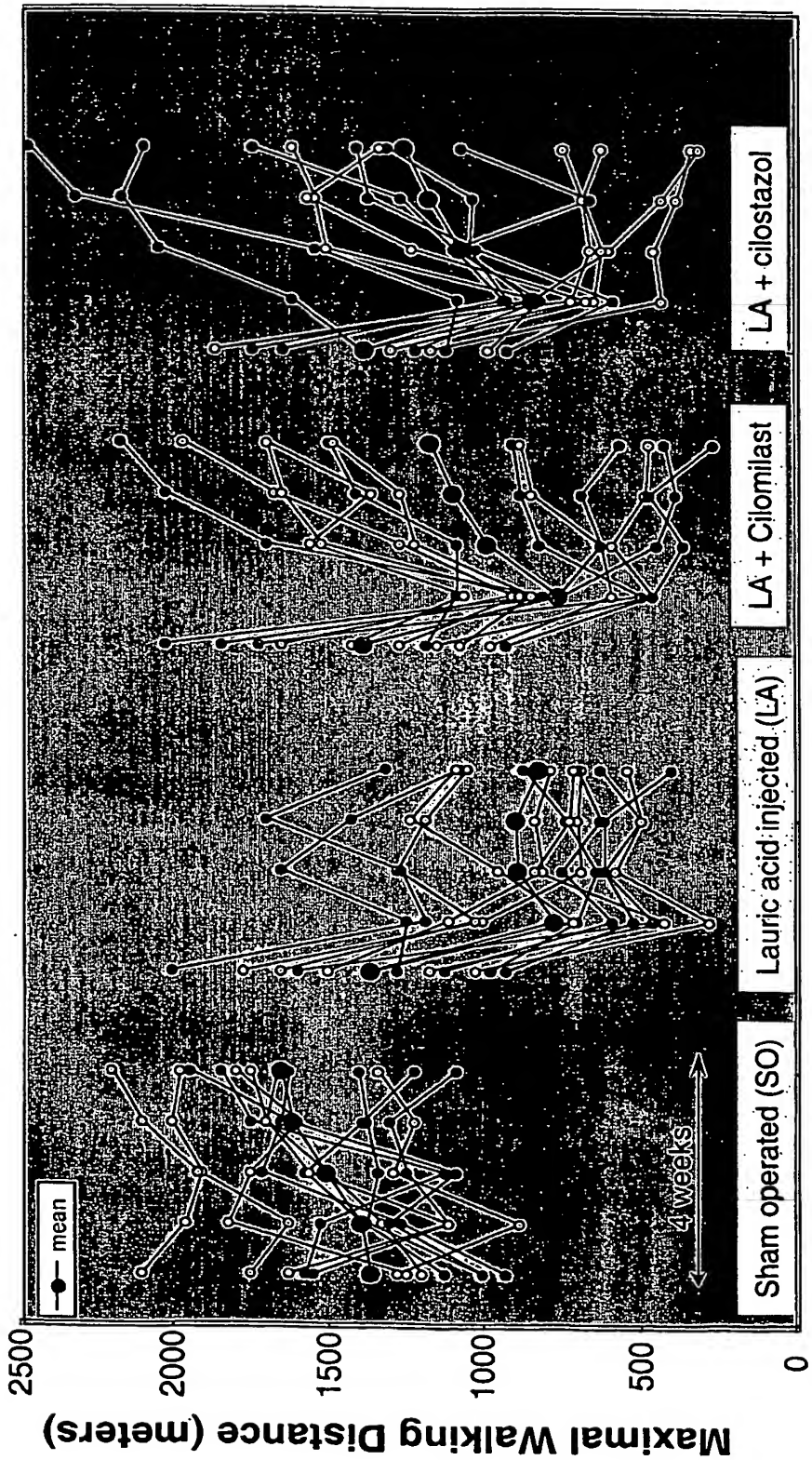
DOUBLE BLIND STUDY

Figure 7



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Figure 8
Individual Results*



*N = 12 rats per group

Figure 9

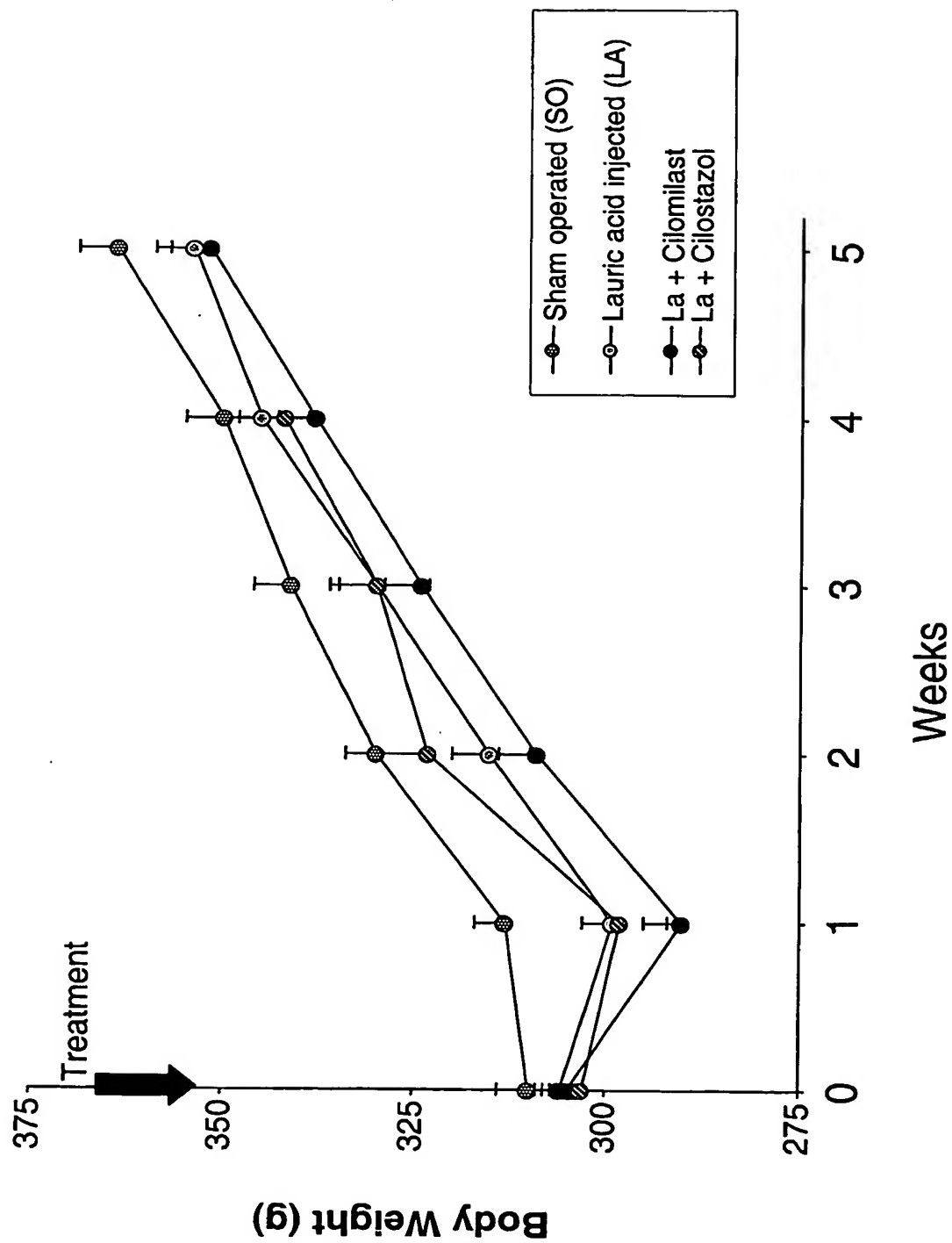


Figure 10

Sham Operated + Vehicle					Lauric Acid Injected + Vehicle				
Rat No	week 1	week 2	week 3	week 4	Rat No	week 1	week 2	week 3	week 4
8					22				
14					26				
15					27				
48					37				
57					39				
61					42				
76					54				
75					65				
80					67				
82					69				
92					98				
100					101				
Lauric Acid injected + Cilomilast					Lauric Acid injected + Cilostazol				
Rat No	week 1	week 2	week 3	week 4	Rat No	week 1	week 2	week 3	week 4
11					4				
21					18				
23					20				
25					34				
35					47				
44					54				
48					59				
49					60				
50					74				
56					78				
71					96				
81					99				

Figure 11

